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TECHNICAL NOTE

A simple and accurate method to determine equilibrated post-dialysis urea concentration

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Fractional urea clearance or Kt/V is usually determined from a two-point method using pre- and post-dialysis blood urea concentrations [1, 2]. Kt/V then becomes critically dependent upon post-dialysis urea concentration [3]. Since immediate post-dialysis urea sampling does not account for recirculation and rebound, it tends to overestimate hemodialysis efficiency [4]. This may occur especially with short, highly efficient modalities [5–8]. A delayed post-dialysis urea determination allows a more accurate estimation of the effective dialysis dose.

Thus, special attention must be paid to sample timing for post-dialysis urea concentration. Shortly-delayed blood sampling (2 min after the end of the session) should correct for vascular access and cardiopulmonary recirculation [9]. However, the internal resistance to urea transfer from different compartments, which explains a large part of the observed urea rebound, is further delayed [10, 11]. Consequently, late blood sampling (30 to 45 min after the end of the session) has been recommended to obtain an equilibrated urea concentration, but such a delay is inconvenient in routine clinical practice.

To overcome this problem, Smye et al have suggested a third early intradialytic blood sample for urea (70 to 90 min from the beginning) that may be used to calculate equilibrated post-dialysis urea concentration [12]. Indeed, the Smye model has proven accurate in the prediction of equilibrated urea [13, 14]. However, the requirements of this approach (a third blood sample and mathematical calculation) may limit its clinical application.

In a previous study concerning the determination of urea rebound using an on-line urea sensor on the ultrafiltrate outflow, the following observations were made: (1) rebound amplitude increased with session efficiency; (2) urea concentration reached a plateau 30 minutes post-session; (3) intradialytic urea concentration 30 minutes before the end of the session was equivalent to the post-dialysis equilibrated value. The present study was undertaken to validate this last observation [15].

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Methods

Patients

Ten stable end-stage renal disease patients regularly treated in our unit were involved in this study after informed consent. Seven males and three females, with a mean age of 52.7 ± 17.4 years and a mean dry body wt of 70.2 ± 6.3 kg, were included. They all had arteriovenous fistulas able to deliver blood flows up to 400 ml/min.

Hemodiafiltration

Hemodiafiltration was performed using the Multimat dialysis machine (Bellco-Sorin, Mirandola, Italy) modified to deliver ultrapure dialysate and with an integrated Urea Monitoring System (UMS, Bellco-Sorin). The substitution fluid, derived from ultrapure dialysate, was produced on-line in a two-stage filtration process (ultrafilter and microfilter) and was subsequently infused into the venous drip chamber (post-dilution). In paired filtration dialysis system, a double-chamber hemodiafilter splits convective and diffusive fluxes in such way that the ultrafiltrate comes out separately [16]. The urea concentration in the ultrafiltrate is basically equivalent to that of arterial blood water [17]. The used hemodiafilters were either Spiraflo SG30 (Bellco-Sorin; consisting of a 0.55 m^2 polysulfone membrane hemofilter followed by a 1.35 m^2 low-flux polysulfone hemodialyzer) or the combination of a HFT05 high-flux polysulfone 0.55 m^2 hemofilter (Bellco-Sorin) followed by a high-flux 1.8 m^2 polysulfone hemodialyzer HF80 (Fresenius, Bad Homburg, Germany). Anticoagulation was achieved with standard heparin administered as an initial intravenous bolus followed by continuous infusion until one hour before the end of the session. For all patients, hemodiafiltration was performed thrice weekly over a fixed duration of 180 minutes followed by 60 minutes of isolated ultrafiltration at a low rate of 30 ml/min. While keeping the session duration constant, at least three different efficiency regimens were applied for each patient: session 1, low range Kt/V; session 2, medium range Kt/V; session 3, high range Kt/V. The operational conditions were adapted to reach these targets, as described below. Desired weight loss was achieved by varying the amount of substitution fluid since the ultrafiltration was always maintained at a constant rate.

Low range Kt/V. This was defined as a blood flow rate of 200 ml/min, dialysate flow rate of 500 ml/min, and an ultrafiltration rate of 50 ml/min; the hemodiafilter total surface area was 1.90 m^2.

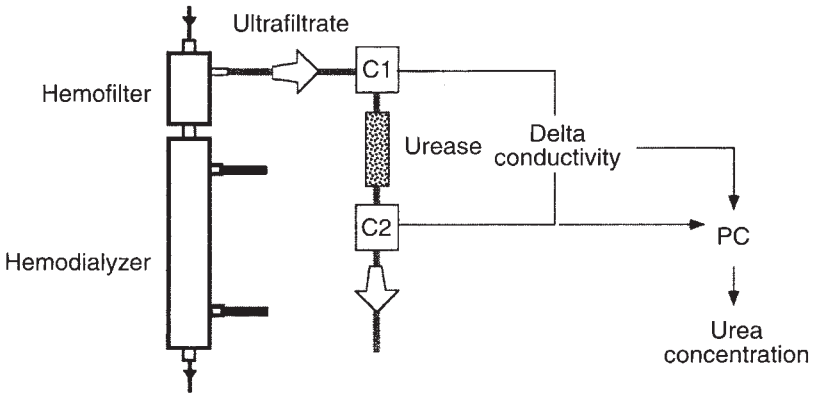

Fig. 1. *Urea monitoring system UMS (Bellco-Sorin).* The dual-chamber hemodiafilter is shown. The UMS integrated in the Multimat dialysis machine is connected to the ultrafiltrate outflow line where it measures urea concentration as described.

Medium range Kt/V. The medium range Kt/V was the same as above, except with a blood flow rate of 400 ml/min.

High range Kt/V. This was defined as a blood flow rate of 400 ml/min, dialysate flow rate of 700 ml/min, ultrafiltration rate of 50 ml/min, and total surface area of the hemodiafilter 2.35 m^2.

Technique for urea monitoring

Intra- and post-dialytic urea concentration was monitored continuously with the UMS placed on the ultrafiltrate outflow of the hemodiafiltration circuit (Fig. 1). This integrated on-line urea monitoring device sensed urea concentration from the rise in conductivity following total urea degradation in its urease cartridge. An algorithm converted the conductivity increase into ultrafiltrate urea concentration, which also reflected serum urea concentration [17]. Continuous urea monitoring was performed over the entire hemodiafiltration session and continued over the 60-minute post-dialytic period of isolated ultrafiltration, and was repeated in each patient for the three defined efficiency regimens.

Calculations and statistics

Kt/V was calculated according to the equation proposed by Garred, Canaud and McCready [18], either accounting for the post-dialysis rebound or not. In this equation, Kt/V corresponds to the negative of slope of the natural logarithm of ultrafiltrate urea concentrations $[urea]_{UF}$ measured continuously versus time, and is corrected for volume contraction and intradialytic urea generation.

$$Kt/V = \frac{-\,LnR\, -\, 3\Delta BW/BW}{1\, -\, 0.01786\,t} \qquad \text{(Eq. 1)}$$

where LnR, BW, ΔBW, and t represent respectively the slope of the natural logarithm of urea concentration decline measured continuously in the ultrafiltrate, dry body wt (in kg), pre- to post-dialysis decrease in body wt (in kg), and dialysis time (in hours). Normalized protein catabolic rate (nPCR) was calculated as suggested by Garred et al [19]. Urea rebound, in %, was calculated as:

$$\text{Rebound} = \{[urea]_{UF\ post\ 30} - [urea]_{UF\ post}\}/[urea]_{UF\ post} \times 100 \qquad \text{(Eq. 2)}$$

where $[urea]_{UF\ post}$ and $[urea]_{UF\ post\ 30}$ represent urea concentrations in the ultrafiltrate immediately after and 30 minutes post-hemodiafiltration. The "total" recirculation, in %, rate was approximated as follows:

$$\text{Recirculation} = \{[urea]_{UF\ post\ 2} - [urea]_{UF\ post}\}/[urea]_{UF\ post} \times 100 \qquad \text{(Eq. 3)}$$

where $[urea]_{UF\ post\ 2}$ is for urea concentrations in the ultrafiltrate two minutes post-hemodiafiltration.

The difference between single-pool Kt/V and equilibrated Kt/V (obtained with the estimate of equilibrated urea concentration 30 min before the end of hemodiafiltration) was compared to the equations proposed by Daugirdas and Schneditz [20] and by Tattersall et al [21] for the estimation of delta Kt/V.

The paired Student's *t* test was applied for statistical analysis with a *P* value of 0.05 considered significant. Results are expressed as mean ± SD values.

Results

A total of 38 hemodiafiltration sessions at the various Kt/V levels were performed. Post-dialysis urea rebound occurred after all of them, its amplitude increasing with the efficiency of the session (Fig. 2). Mean rebound values reached approximately 14, 24 and 28% with respective mean Kt/Vs of 0.78 ± 0.17, 1.26 ± 0.12 and 1.70 ± 0.14, or mean K/V values (per hour) of 0.26 ± 0.05, 0.42 ± 0.04 and 0.57 ± 0.03. For the three subgroups, the urea concentration 30 minutes after hemodiafiltration was compared to the concentration measured 30 minutes later (at 60 min); no significant difference was noted confirming that the urea rebound is complete 30 minutes post-session. Estimated mean total recirculation (from the vascular access and cardiopulmonary bypass) was 4.4 ± 2.0%, with respective values of 4.1 ± 1.5, 4.4 ± 2.6, and 5.5 ± 1.0% for the low, medium, and high efficiency sessions. Mean nPCR for the whole group was 0.9 ± 0.3 g/kg/day.

Figure 3 is a typical example of the evolution of intra and post-dialytic urea concentrations as monitored by the UMS. The tracings, obtained for one patient with the three different efficiency regimens, illustrate the main findings of our study: first, as expected, the decline in $[urea]_{UF}$ varies with session efficiency (slope or K/V); second, post-dialysis urea rebound reaches a plateau 30 minutes after the end of hemodiafiltration; third, the equilibrated urea concentration (30 min post-session or at the plateau) corresponds to the concentration observed 30 minutes

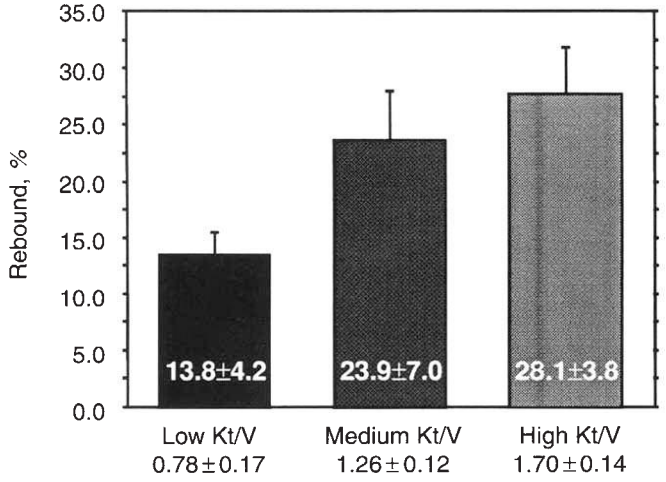

Fig. 2. *Mean urea rebound (in % ± SD) for the three different hemodiafiltration efficiency regimens.*

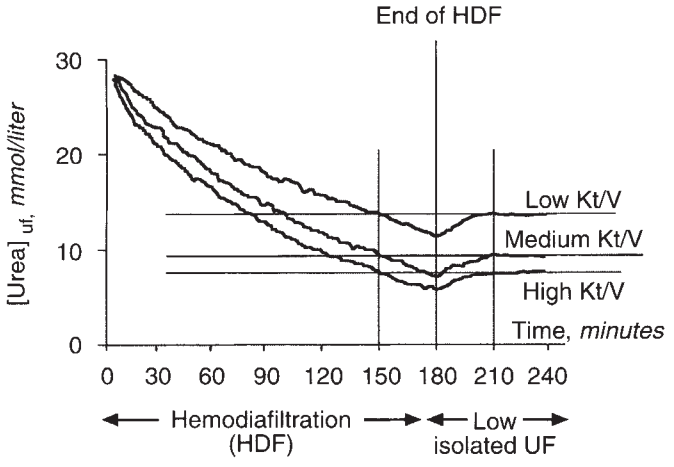

Fig. 3. *Typical evolution of intra- and post-dialytic urea concentration in the ultrafiltrate as recorded by the UMS for three variable efficiency sessions in one patient.*

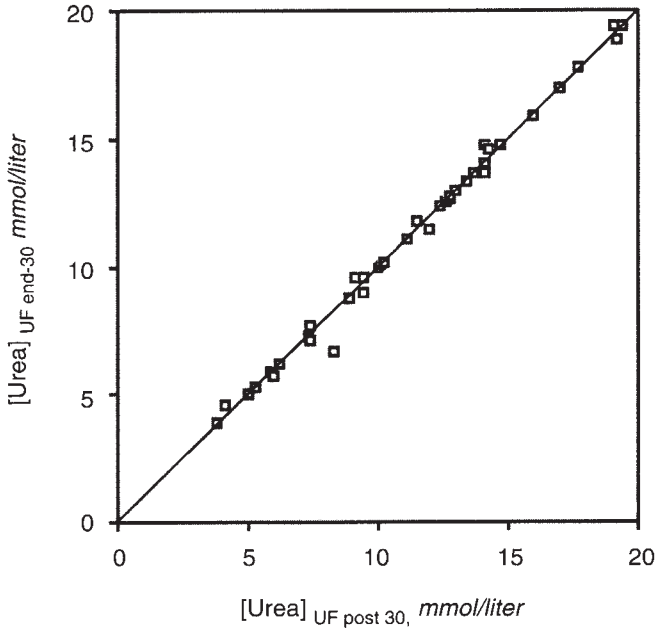

Fig. 4. *Relationship between urea concentrations measured in the ultrafiltrate by UMS 30 minutes before the end and 30 minutes post-session for 38 hemodiafiltration treatments.* The correlation coefficient is 0.996; 95% confidence limits are 11.059 and 11.294. y = 1.005x − 0.0715; $P < 0.001$. The diagonal line is the identity line.

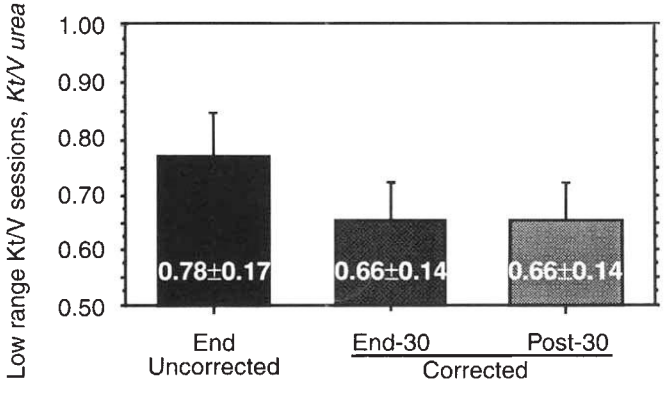

Fig. 5. *"Uncorrected" and Kt/V "corrected" for rebound obtained with the low range efficiency sessions.* "Corrected" Kt/V was calculated with urea 30 minutes post-session or its estimate 30 minutes before the end of the session.

before the end of the session. This last observation is valid over the entire spectrum of intensity regimens evaluated.

For each session, urea concentration 30 minutes before the end of hemodiafiltration ($[urea]_{UF\ end\text{-}30}$) was compared to equilibrated urea concentration (30 min post-hemodiafiltration or $[urea]_{UF,\ post\ 30}$); a highly significant linear correlation ($r = 0.996$) is shown in Figure 4. When considered by efficiency subgroups, mean urea concentration 30 minutes post-session (14.2 ± 3.1, 9.4 ± 2.7 and 5.1 ± 1.4 mmol/liter) was nearly identical to urea concentration measured 30 minutes before the end (respectively, 14.2 ± 3.1, 9.3 ± 2.8 and 5.3 ± 1.4 mmol/liter).

Kt/V was obtained from the slope of $[urea]_{UF}$ decline versus time for the three different efficiency regimens. In addition, Kt/V values calculated with immediate post-dialysis urea ("uncorrected or single-pool Kt/V") were compared to those calculated with equilibrated post-dialysis urea concentration or its estimate 30 minutes before the end (equilibrated Kt/V); results are presented in Figures 5, 6, and 7. The "uncorrected" Kt/V values were approximatively 15% higher than those corrected for rebound. The Kt/V values calculated either with equilibrated urea concentration or its estimate correlated closely (Fig. 8), supporting the validity of our method for calculating equilibrated or double-pool KtV.

The mean delta Kt/V (difference between single-pool and equilibrated Kt/V) using $[urea]_{UF\ end\text{-}30}$ for the three efficiency regimens (low, medium, and high range) were respectively 0.12 ± 0.04, 0.20 ± 0.03, and 0.28 ± 0.03. These differences were compared to the delta Kt/V (single-pool minus equilibrated)

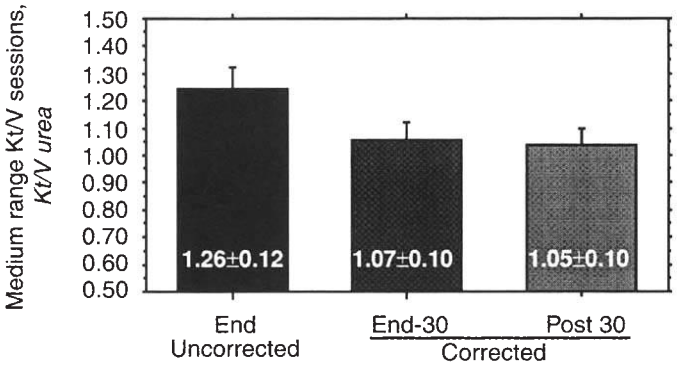

Fig. 6. *"Uncorrected" Kt/V and Kt/V "corrected" for rebound obtained with the medium range efficiency sessions.* "Corrected" Kt/V was calculated with urea 30 minutes post-session or its estimate 30 minutes before the end of the session.

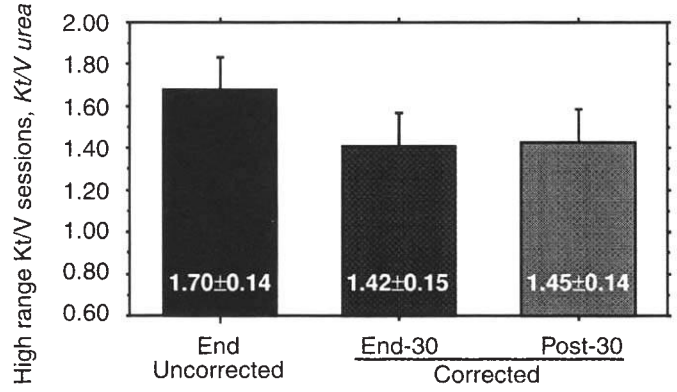

Fig. 7. *"Uncorrected" Kt/V and Kt/V "corrected" for rebound obtained with the high range efficiency sessions.* "Corrected" Kt/V was calculated with urea 30 minutes post-session or its estimate 30 minutes before the end of the session.

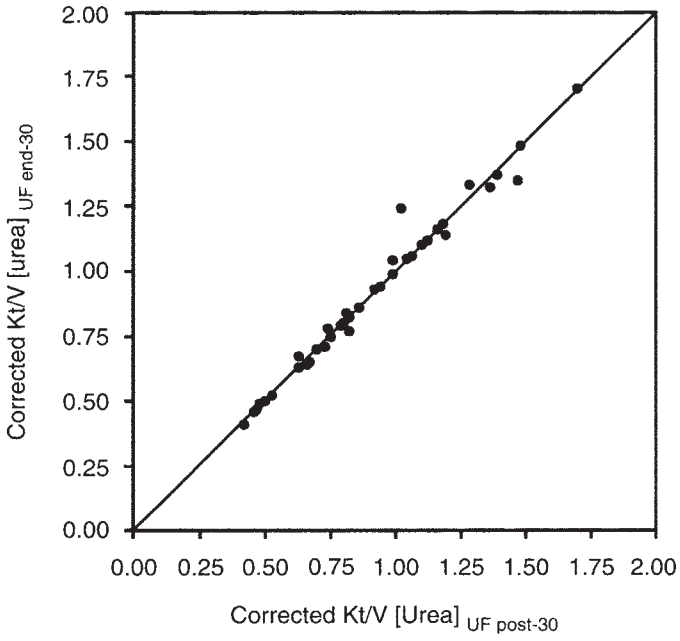

Fig. 8. *Relationship between the two methods used to calculate Kt/V accounting for rebound, either with urea concentration 30 minutes post- or 30 minutes before the end of hemodiafiltration.* The obtained correlation coefficient is 0.998; 95% confidence limits are 0.891 and 0.927.

estimated with the equation from Daugirdas and Schneditz [20], and with the equation from Tattersall et al [21] for each session; the results are shown in Figure 9.

Discussion

Estimating the effective "dialysis dose" delivered to a patient should account for the multicompartment urea kinetics within the body [22]. Urea rebound, consequent to this latter phenomenon, significantly alters post-dialysis urea concentration, therefore affecting "dialysis dose" estimation. Indeed, the immediate post-dialysis or non-equilibrated urea concentration overestimates the delivered dose [23, 24], whereas the equilibrated or delayed concentration allows a more accurate assessment. An equilibrated urea sample, obtained by waiting an extra 30 minutes after the session, is inconvenient to patients and care providers. Alternative methods to estimate dialysis dose delivery more precisely have been proposed, such as direct dialysis quantification, by either total or partial dialysate collection, and by on-line urea monitoring [25–28].

Compared to initially released simplified formulas based on pre- and post-dialysis urea concentrations, the last generation of equations incorporates correction factors for extracellular volume contraction and urea generation during dialysis [29]. Despite such an improvement, their accuracy still depends significantly on post-dialysis urea sample timing. Thus, equilibrated post-dialysis urea concentration remains a key parameter for precise dialysis quantification even when using simple urea kinetic modeling. Smye et al have proposed a reliable method to calculate equilibrated urea concentration [6, 13], but its clinical application has been limited by the necessity of a third blood sample.

We propose a new, simple, and cost-effective method to predict post-dialysis equilibrated urea concentration. Continuous urea monitoring on the ultrafiltrate outflow confirmed that post-dialysis urea rebound is complete at 30 minutes. Interestingly, it also showed that equilibrated urea concentration (30 min after the session) is equivalent to urea concentration 30 minutes before ending the session. This last observation has been validated prospectively in 38 hemodiafiltration sessions over a wide range of dialysis efficiency; therefore, it should be equally reliable when applied to other dialytic modalities. Recently, a real-time two-pool urea kinetic simulation system was implemented on a paired filtration dialysis fitted with an on-line urea concentration sensor, with the purpose of validating our observation [30, 31].

As shown, Kt/V uncorrected for rebound significantly overestimated effective dialysis dose, particularly with high efficiency regimens, whereas, the use of either equilibrated urea concentration or its estimate 30 minutes before the end of the session allowed accurate estimation of double-pool Kt/V. Furthermore, the differences between single-pool and equilibrated Kt/Vs obtained with urea 30 minutes before the end of the session were close to identity when compared to those obtained when using the

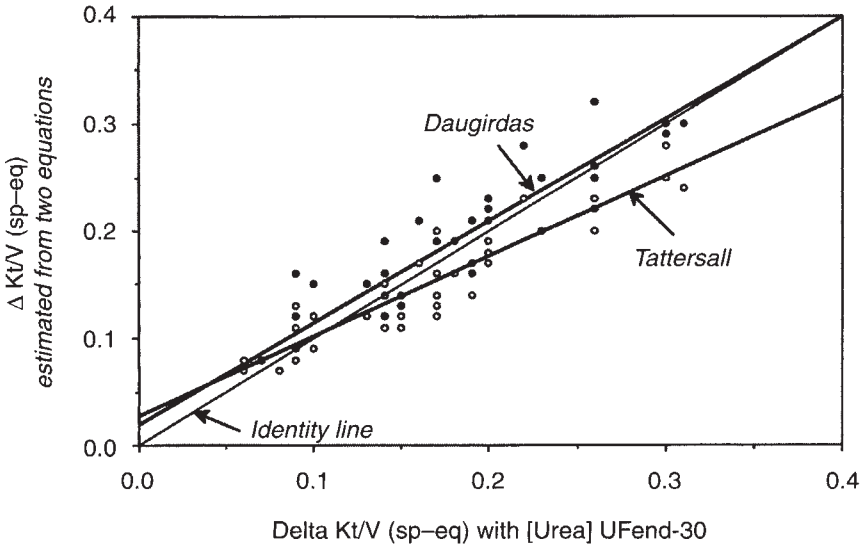

Fig. 9. *Relationship between delta Kt/V (difference between single-pool (sp) and equilibrated (eq) values) when using urea concentration 30 minutes before the end versus delta Kt/V when using the Daugirdas and Schneditz equation [20] (●) or the Tattersall et al equation [21] (○).* Respective correlation coefficients are 0.919 ($P < 0.0001$) and 0.934 ($P < 0.0001$), whereas the respective lower and upper 95% confidence limits are 0.174–0.193 and 0.148–0.161.

formulas from Daugirdas and Schneditz [20] and from Tattersall et al [21].

In conclusion, equilibrated post-dialysis urea concentration accounting for rebound may be accurately predicted by the urea concentration obtained 30 minutes before the end of the session, as demonstrated by on-line urea monitoring. It has two major advantages: first, it obviates the necessity to wait an extra 30 minutes after treatment for a delayed sample; second, it avoids the third intradialytic blood sampling required when applying the Smye method since only two blood samples suffice with this approach.

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